REMARKS

Claims 1-9, 11, 13-17, and 46 are pending in the application. Withdrawn claim 54 has been canceled, without prejudice to its inclusion in one or more related applications, in view of the final Restriction Requirement, as the Examiner has withdrawn this claim from further consideration, 37 C.F.R. § 1.142(b) as being drawn to a non-elected invention. Applicant notes the Examiner has withdrawn rejection of claims 1-11, 13-17 and 46 for inadequate written description under 35 U.S.C. § 112 first paragraph.

Claims 1-9, 11, 13-17, and 46 stand rejected.

Rejection Under the First Paragraph of 35 U.S.C. § 112.

The Examiner has rejected claims 1-11, 13-17, and 46 under 35 U.S.C. § 112, first paragraph, asserting that the claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Applicant traverses each of these grounds of rejection.

Specifically, the Examiner has alleged lack of enablement on the following grounds:

1. while being enabling for a method of *in vitro* generation of a differentiation mammalian cells, wherein differentiated mammalian cells is selected from the group consisting of a skeletal muscle, endothelial, and hematopoietic cell, comprising maintaining an isolated human KDR+ stem cells in the medium in the presence of the differentiated mammalian cell, the specification does not reasonably provide enablement for a method of *in vivo* generating a differentiated human cell of any selected type;

2. asserting that Waller et al. concludes there is no evidence that a single cell can differentiate along both hematopoietic and stromal lineage, the specification allegedly does not make clear how the injected human donor post natal $CD34^{+}KDR^{+}$ cells differentiated into any specific cell type as claimed in claim 17;

3. it is "very possible" that the cell population contain heterogeneous cell population of $CD34^{+}KDR^{+}$ cells give rise to both hemopoietic and stromal elements, thus it is allegedly "not clear" from the specification, "how homogenous" the population of natal $CD34^{+}KDR^{+}$primitive stem cells is;

4. in regards to point 3 above, there is no evidence that there was no fusion of the $CD34^{+}KDR^{+}$ cells with cells of other lineages as described by Holden et al;

In view of the positions noted above, the Examiner concluded:

> In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

With respect to point (1) above, Examiner has determined that the specification is enabling for *in vitro* generation of differentiated mammalian cells, wherein the differentiated mammalian cells is selected from the group consisting of a skeletal muscle cell, an endothelial cell, and hematopoietic cell, comprising maintaining an isolated human KDR+ stem cells in the medium in the presence of the differentiated mammalian cell. In contrast, Examiner contended that a person of skill in the art would not have understood the applicability of the method *in vitro* to an *in vivo* context. Applicant respectfully disagrees.

The examples themselves and the extensive citation of references in the application relating to the techniques involved would be more than adequate to enable a person having a high level of skill in this art, based on the description in the specification would have understood how to make and use the invention both *in vitro* and *in vivo*. While *in vitro* experimentation is not without limitations, it is often used by those skilled in the art to show what is expected *in vivo*, particularly when extensive *in vivo* testing is not feasible.

With respect to point (2) above, Examiner again relies upon Waller et al. (Blood, 1995 v.85, pp2422-2435) (hereinafter "Waller"), for the proposition that there is no evidence that a single cell can differentiate along both a hematopoietic and stromal lineage (citing page 2434). Applicant respectively disagrees, and again draws Examiner's attention to Example 2 at page 62 of the present application which contains such evidence that $CD34^{+}KDR^{+}$ cells resulted in both hematopoietic and endothelial cell precursors.

Applicant also respectfully submits that reliance on Waller is misplaced, because the unrepresentative nature of the reference is facially apparent. Two of the very same investigators of the Waller study had previously themselves "claimed that a single, common BM stem cell can differentiate along both hematopoietic and stromal lineages...." The reference even begins with a recitation of all the substantial research supporting the common stem cell hypothesis. (Waller at 2422). This shows that those skilled in the art recognize that there *is* evidence that a single cell can differentiate along both hematopoietic and stromal lineages. While Waller may exhibit a

different point of view, it is one not long held at publication, and not necessarily prevalent, particularly considering Waller notes sixteen references which support Applicant's position.

With respect to point (3), Examiner's attention is again directed to paragraph [0069] at page discloses that starvation-resistant cells isolated according to the present invention are essentially 100% KDR^+, and also paragraph [0112] at pages 38-39 of the application states the following with respect to the purity of the isolated KDR^+ cells:

> Isolated KDR^+ cells are preferably present in a population that is at least about 80% KDR^+ cells, and more preferably at least 90% KDR^+ cells. Typically, a population of cells referred to herein as isolated KDR^+ cells means a population in which about 80% to 100% of the cells express the KDR marker. Although cell populations comprising fewer than 80% KDR^+ cells can be used in the methods described herein, the efficiency of the methods will generally decrease as the proportion of KDR^+ cells in the population decreases.

One skilled in the art would understand that the population of isolated KDR^+ cells should be very homogenous, attaining a percentage approaching 100%. Furthermore, the specification also discloses how to achieve such highly homogenous population by the isolation techniques disclosed in paragraphs [0016] and [0028]. This is further supported by Figs. 1E and 1F of the present application which show purity of at least 98% $CD34^+$ cell populations. See the description of these Figs. at paragraph [0032] at page 9 and paragraph [0169] at page 49.

Examiner asserts support for the position that it is "very possible" that the cell population is heterogeneous from Madeddu et al (he FASEB Journal, express article 10.1096/fj.04-2192fje, published online September 2, 2004) which explains the $CD34^+KDR^+$ subset comprises EPC's as well as primitive hematopoietic cells and hemangioblasts. However, this very same reference explains that all three may represent a single cell pool exhibiting hematopoietic and/or endothelial differentiation. And, regardless of what the $CD34^+KDR^+$ subset holds, the specification clearly explains that a homogenous culture is desired, and how to obtain one.

Finally, regarding point (4) above, the Examiner has stated:

Moreover, there is no evidence from the Specification that there <u>was no fusion of the $CD34^+KDR^+$ cells with cells of the other lineages</u>. Holden et al. (Science, 2002, V.296, pages 2126-2129) teach that cells can mutate and develop markers characteristics of other lineages or that cells injected into a foreign tissue can take up local DNA and thus appears to have changes

identify (see page 2126 in particular). Moreover, Holden et al. further teach that fusion scare has given further impetus to effort to establish rigorous standards for demonstrating plasticity such as: the cells must be properly identified at the outset, because a single alien cell in ostensible purified culture could produce misleading results. The cells must contribute to the function of the host tissue. There is no indication that demonstrate functionality of said cells in the specification. [original emphasis]

The Holden article is generally directed to and discusses some perceived flaws in previous research upon which conclusions of cell plasticity have been drawn. The Examiner appears to be questioning whether the differentiation recited in the claim actually occurs, contending that there is no characterization of the resultant cells as to phenotype or functional capacity. Applicant respectfully draws Examiner's attention to Examples 2-5. Not only do these examples support that differentiation recited in the claim actually occurs, there is also no evidence that Applicant's data are flawed. Furthermore, these rigorous standards for plasticity, set forth by three researchers (one of whom is described as the most outspoken skeptic in the field) has not been met by *any* study in the art. To hold Applicant to such a standard that no one in the art has attained, when the population of skilled artisans is not made of these three individuals and their standard has not been widely adopted is clearly inappropriate.

Example 2 shows *in vitro* evidence that the $CD34^+KDR^+$ cells resulted in both hematopoietic and endothelial cell precursors. Likewise, Example 3 at pages 63 – 64 of the application detected hemoangioblasts resulting from $CD34^+KDR^+$ cells, where the hemoangioblasts tested positive for both hematopoietic and endothelial cell markers. Further, Example 4 at pages 64 – 65 of the present application, $CD34^+KDR^+$ cells injected into murine blastocysts resulted in newborn mice having human/mouse chimerism in multiple tissues, including tissue of the central nervous system, (brain and spinal cord) and tissues of endodermic or mesodermic origin (*e.g.* liver, lung, gut, skeletal muscle, heart and kidney). Still further, Example 5 at pages 65 and 66 of the present application showed that $CD34^+KDR^+$ cells or $CD34^-lin^-KDR^+$ cells from peripheral blood and cord blood differentiated into mesenchymal tissues other than the original tissue, and specifically skeletal muscle cells. These examples provide further evidence that the $CD34^+KDR^+$ cells differentiate into other tissues. Patent law does not require an accurate explanation of the theory or mechanism for the functional results as demonstrated in the present application.

In view of the foregoing discussion, it is respectfully submitted that the Examiner's grounds of rejection based upon 35 U.S.C. § 112, first paragraph, for lack of enablement, have been overcome. Reconsideration and withdrawal of the rejection with respect to all claims are respectfully requested.

Rejection Under 35 U.S.C. § 103(a).

The Examiner has rejected claims 1-3, 5-10, 13-17, and 46 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,736,396 of Bruder, *et al.* (hereinafter "Bruder"), taken in view of U.S. Patent No. 5,912,133 of Lemischka (hereinafter "Lemischka"), and in view of the present specification disclosure at page 63, line 48, and page 4, lines 4-10.

Examiner states, "It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '133 to those of US Patent'396 and substitute isolated human mesenchymal stem cells to isolating human KDR^+ stem cells to obtained a claimed method...," and continues "One of ordinary skill in the art at the time the invention was made would have been motivated to do so because isolated human KDR^+ stem cells can be induced to differentiate *in vitro* or *in vivo* and this ability has an important therapeutic application as taught by US Patent '133." Additionally, Examiner contends that "it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention." Initially, Applicant questions how a basis for finding an invention not enabled can then be asserted as apparent, and expected to succeed, to one of ordinary skill in the art. The Examiner cannot reasonably assert these contradictory positions.

Regardless, the Examiner asserted that '396 teaches a method of generating a differentiated cell of a selected type by incubation of human mesechymal stem cells in the presence of differentiating mammalian cells or a "conditioned medium" that are effective to induce the differentiation into a lineage of choice. The Examiner conceded that '396 does not teach that the stem cells are human KDR^+ stem cells, but rather '133, teaches a method of isolating human FLK^+ stem cells using an antibody that specifically binds FLK-1 *and* that human KDR^+ cells are the "same subpopulation" of $CD34^+$ cells as "human FLK^+ stem cells." Thus, the Examiner reasons that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of '396 to that of '133 to substitute isolated

human mesechymal stem cells with isolated human KDR^+ stem cells to obtain the claimed method.

Applicant again respectfully traverses the rejection.

Integral to the Examiner's argument is that human KDR^+ cells are the "same subpopulation" of $CD34^+$ cells as "human FLK^+ stem cells." However, this is not found in either cited reference '133 or '396. The Examiner does not argue that this is a generally known concept in the art. Rather the Examiner cites Applicant's own specification, which is an improper source for reliance. The Examiner made an obviousness rejection. Because the references cannot support a rejection based on anticipation or lack of novelty, a combination of references is required with a motivation to combine. Here, the motivation to combine appears to have been based on the hindsight provided by Applicant's own application, as the Examiner has specifically relied on two statements from the application. Such a combination, in the absence of any other motivating factor appears to be both unreasonable and inappropriate in supporting an obviousness rejection. Once an applicant discloses his or her invention the disclosure itself cannot reasonably be relied upon to support a combination of other references.

Here, one must objectively ask why a person skilled in the art, in the absence of the present disclosure, would combine the references. While they both relate to identification and characterization of stem cells and the desirability that the stem cells be used therapeutically if and when they differentiate into other tissues, they do not teach or suggest a method involving the isolation or use of KDR^+ stem cells. The objective analysis is especially important to keep from slipping, even inadvertently, into a hindsight obviousness analysis, which is not allowed.

Thus, when objectively analyzing the teaching of the references, it is important to understand what each teaches, and that each teaches something other than what Applicant is claiming in the present application. The combination of different teachings cannot result in Applicant's invention in the absence of the hindsight provided only by Applicant's own disclosure. Each reference approaches its issue differently from each other and from Applicant's method, as explained in detail in Applicant's response filed January 29, 2004, which will not be repeated here, but is incorporated by reference herein. One skilled in the art, having both references before him or her, among the myriad references that exist, would not come to a realization absent the spark provided only by Applicant that their distinct teaching should be combined in any way, let alone in a way that assertedly renders Applicant's invention obvious.

To do so ignores the separate teachings of each reference. Only an artificial combination is possible and that is inappropriate for supporting an obviousness rejection.

Reconsideration and withdrawal of the obviousness rejection is respectfully requested.

Since all of the grounds for rejection have been overcome, Applicant respectfully solicits an early Notice of Allowance of all claims.

Respectfully submitted,

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Enclosure:
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